

Case Report

Vagus nerve stimulation in Lafora body disease[☆]

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ABSTRACT

Introduction: Lafora body disease (LBD) is a rare autosomal recessive disorder characterized by progression to inexorable dementia and frequent occipital seizures, in addition to myoclonus and generalized tonic–clonic seizures (GTCSs). It belongs to the group of progressive myoclonus epilepsies (PMEs), rare inherited neurodegenerative diseases with great clinical and genetic differences, as well as poor prognosis. Since those patients have a pharmacoresistant disease, an adjunctive treatment option is vagus nerve stimulation (VNS). To date, there are four reported cases of the utility of VNS in PME – in Unverricht–Lundborg disease (ULD), myoclonic epilepsy with ragged-red fibers (MERRF), Gaucher's disease, and in one case that remained unclassified.

Case presentation: A 19-year-old male patient had progressive myoclonus, GTCSs that often progressed to status epilepticus (SE), progressive cerebellar and extrapyramidal symptomatology, and dementia, and his disease was pharmacoresistant. We confirmed the diagnosis of LBD by genetic testing. After VNS implantation, in the one-year follow-up period, there was a complete reduction of GTCS and SE, significant regression of myoclonus, and moderate regression of cerebellar symptomatology.

Conclusion: To our knowledge, this is the first reported case of the utility of VNS in LBD. Vagus nerve stimulation therapy may be considered a treatment option for different clinical entities of PME. Further studies with a larger number of patients are needed.

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1. Introduction

Lafora body disease (LBD) is a rare autosomal recessive disorder first described by Lafora and Gluelkin in 1911, with onset between the ages of 10 and 18 years, characterized by progression to inexorable dementia and frequent occipital seizures, in addition to myoclonus and generalized tonic–clonic seizures (GTCSs). Distinctive features of the disease include polyglucosan inclusions (Lafora bodies) in the neurons and various other tissues, including the skin, the skeletal muscles, and the heart. The disease is connected with mutation of the two genes located on chromosome 6q24, involved in the glycogen metabolism of EPM2A (encoding protein tyrosine phosphatase – laforin) and EPM2B (encoding protein

ubiquitin ligase – malin). Recently, a mutation of the third gene EPM2C has also been identified [1].

Lafora body disease belongs to the group of progressive myoclonus epilepsies (PME), rare inherited neurodegenerative diseases with poor prognosis that account for around 1% of epilepsy cases at specialist centers. Progressive myoclonus epilepsies encompass different diagnostic entities and common causes. Besides LBD, they include Unverricht–Lundborg disease (ULD), myoclonic epilepsy with ragged-red fibers (MERRF), neuronal ceroid lipofuscinoses, sialidoses, and dentatorubral-pallidoluysian atrophy [2,3]. Since those patients have a pharmacoresistant disease and are not candidates for resective neurosurgical treatment, adjunctive treatment options are vagus nerve stimulation (VNS) and subthalamic deep brain stimulation (DBS) [4]. To date, there are four reported cases of the utility of VNS in PME – in ULD, MERRF, Gaucher's disease type III, and one case that remained unclassified (the last patient also underwent DBS after VNS) [5–7]. We report a first case, to our knowledge, of the utility of VNS in LBD.

2. Case presentation

A 19-year-old patient was hospitalized for the first time at our hospital in May 2012. Disease onset was at the age of 16, with occipital elementary partial seizures and bilateral hand myoclonus that, after a few

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Table 1
Nucleotide sequence of the primers used for PCR amplification.

Primer	Sequence
EPM2B F1	5'-TGACCATGACTGTGACCGTGA-3'
EPM2B F2	5'-GGTGTGCACCTCATAGAGCT-3'
EPM2B F3	5'-ATGTCACCATCACCAACGACT-3'
EPM2B F4	5'-TCAAGTATGCAGCTTGTCCGC-3'
EPM2B R1	5'-GCTGAGCCAGGAGCTCTATG-3'
EPM2B R2	5'-GACAACCACATGGCAGTCGTT-3'
EPM2B R3	5'-AGGTATCCACTGGCCGACAA-3'
EPM2B R4	5'-ACAATTCAATATGGCAGCACTAGTG-3'

months, progressed to generalized myoclonus, which occurred on a daily basis, often in clusters (provoked with sleep deprivation and video games). In addition, he had GTCS that occurred every 2 to 3 months and often progressed to status epilepticus (SE). In the subsequent three years, he also developed progressive cognitive decline – dementia (Mini Mental State Examination – MMSE 15) – as well as cerebellar and extrapyramidal symptomatology (moderately severe dysarthria, square wave jerks of extraocular movements, fine tremor of eyelids and lips, truncal and limb ataxia, bradykinesia, and generally increased muscle tone – rigidity). The patient's disease was pharmacoresistant, with a seriously diminished quality of life.

We performed extensive diagnostic evaluation from which we point out the most important findings: electroencephalogram revealed electrographic status epilepticus – paroxysmal discharges of high-amplitude spike/slow waves and polyspike/waves almost every second, more pronounced during photic stimulation; brain magnetic resonance imaging (MRI) showed diffuse brain atrophy; electromyoneurography revealed mild generalized myopathy with hypersynchronous potentials, in correlation with myoclonic jerks; cerebrospinal fluid analysis,

metabolic tests, and muscle biopsy as well as biopsy of axillary skin and peripheral nerve studies were normal.

To confirm putative genetic mutation, genomic DNA was extracted from a peripheral blood sample using a Gentra Puregene Blood DNA purification kit (Qiagen Inc., Valencia, CA, USA). The entire coding and flanking sequences (single exon) of the EPM2B gene were amplified by polymerase chain reaction (PCR). Four primer pairs produced four overlapping PCR fragments spanning the whole EPM2B exon, including the flanking noncoding sequences (Table 1). The amplified fragments were analyzed by agarose gel electrophoresis, purified using the PCR Purification Kit (Qiagen) and sequenced on a 3730XL DNA Analyzer (Applied Biosystems). The results were analyzed with the Mutation Surveyor Software (SoftGenetics). Our analysis identified causative mutation for the LBD in the EPM2B gene c.992delG (homozygous) (Fig. 1). Another polymorphism without clinical relevance was rs10949483 (homozygous). In order to confirm the detected mutation, samples from both parents were analyzed. The analysis determined that both parents were heterozygous carriers of the EPM2B gene mutation c.992delG (Fig. 1).

At that time, the patient was treated with five antiepileptic drugs (AEDs): levetiracetam (2500 mg), valproic acid (2000 mg), metilphenobarbiton (100 mg), clonazepam (4 mg), and acetazolamide (750 mg), as well as L-carnitine. In agreement with his parents, we decided to implant a vagus nerve stimulator (Cyberonics; Houston, Texas, USA). One week after implantation, VNS was initiated at 0.25 mA and gradually increased in the following months to 2 mA. The duty cycle was on the basis of controlled clinical trials set to a 30-Hz signal frequency, a 500-ms pulse width, 30 s of on-time, and 3 min of off-time [8]. Considering the persistence of myoclonus after 6 months, we performed a stimulation scheme under which the principal duty cycle was set to 44% (parameters were gradually changed every three weeks: first, 21 s of on-time and 1.1 min of off-time, then 7 s of

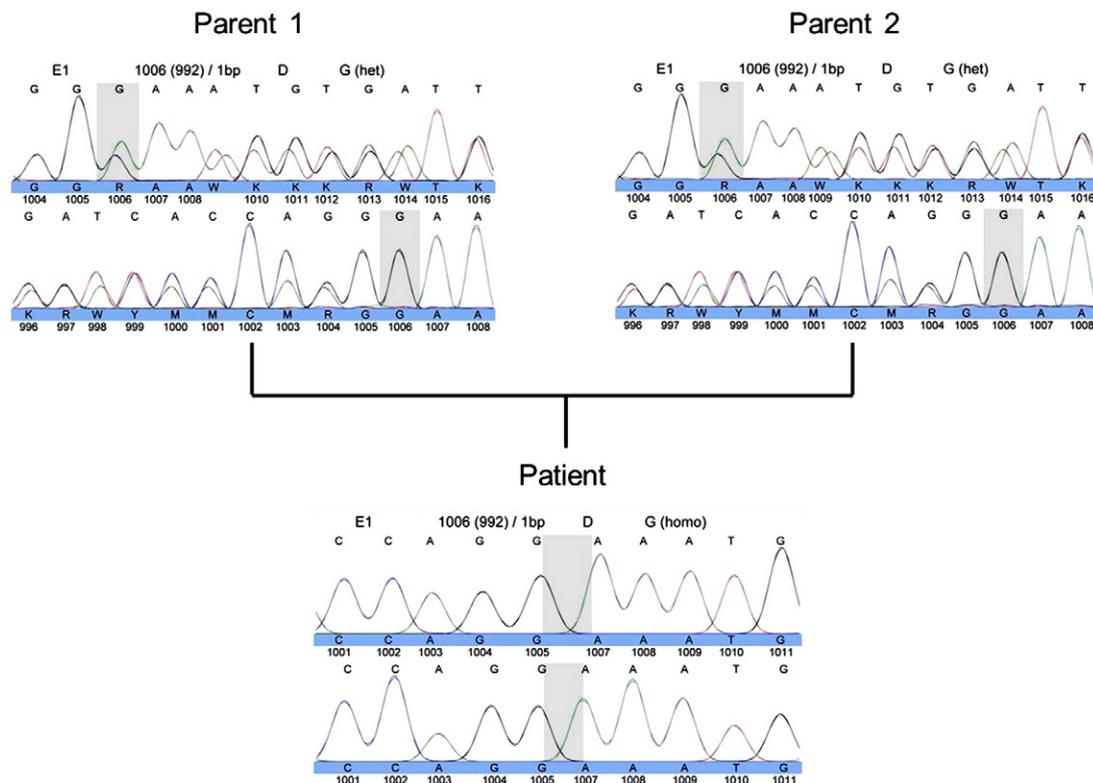


Fig. 1. Causative mutation for the Lafora body disease in the EPM2B gene c.992delG (homozygous) demonstrated in the patient. Both parents are heterozygous carriers of the EPM2B gene mutation c.992delG.

on-time and 0.5 min of off-time, with the following final parameters – 7 s of on-time and 0.3 min of off-time for three months). After VNS implantation, we did not reduce the dose and number of AEDs. In the one-year follow-up period, the patient's clinical condition and quality of life improved. There was significant regression of myoclonus (myoclonus is less frequent, on a weekly basis, limited to the hands, and no longer occurs in clusters) and moderate regression of cerebellar symptomatology, and, following VNS implantation, the patient did not experience GTCs or SE. The patient did not report any significant side effects of the VNS; however, he complained about transient mild hoarseness after the neurosurgical procedure.

3. Discussion and conclusion

Our case suggests that VNS may have utility in patients with LBD. The efficacy of adjunctive VNS is well established in adults and adolescents with partial epilepsy with or without secondary generalization, as well as in patients with Lennox–Gastaut syndrome [9–11]. According to the four published cases in the literature so far, VNS has also been shown to be useful for GTCs and SE in patients with PME – ULD, MERRF, and Gaucher's disease (with the last disease being a rarer case of PME). However, in three of those cases, VNS did not control myoclonus, cerebellar symptoms, and mental retardation. Like the patients studied in the literature, our patient was followed for one year and benefited from VNS with marked reduction of GTCs and SE. In addition, our patient showed reduction of myoclonus and improvement in cerebellar abnormalities. The explanation could lie not only in the different etiology of PMEs but also in the differences in VNS parameter settings between the patients. In the two recently published cases by A. Fujimoto et al. [7] (one case with MERRF and one case with Gaucher's disease), the duty cycle was set to a 30-Hz signal frequency, a 500-ms pulse width, a 30-second on-time, and a 5-minute off-time. In our patient with LBD, we managed to reduce the myoclonus by gradually changing the duty cycle to 7 s of on-time and 0.3 min of off-time (other parameters such as signal frequency and pulse width were the same in all three patients). The final dosing increments of VNS in our patient and in the other two patients were 2 mA, 1.25 mA, and 1.5 mA, respectively.

We want to emphasize the positive effects of VNS for patients with LBD in reducing GTCs, status epilepticus, myoclonus, and cerebellar symptoms. To our knowledge, this is the first such reported case. Vagus nerve stimulation therapy may be considered a treatment option for the different clinical entities of PME. Further clinical studies with a larger number of patients are needed to confirm the clinical effects produced by chronic vagus stimulation in patients with progressive myoclonus epilepsies.

Ethics in publishing

All the investigations and treatment of the patient presented in this paper were evaluated and approved by the Ethics Committee of the University Hospital Centre Zagreb, Croatia.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contributions

All authors stated above made substantive intellectual contributions to this published case report. SH treated the patient and wrote the article; ZPG treated the patient and wrote the article; FB performed genetic testing; SN participated in the treatment of the patient and helped to draft the manuscript; GM operated on the patient; KG participated in performing genetic testing; VS participated in the treatment of the patient; IK participated in the treatment of the patient; and ABK helped to draft the manuscript.

All authors read and approved the final manuscript.

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